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On Some Fallacies Inherent in the Parasitic Theories of the Etiology of Carcinoma.

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ON SOME FALLACIES INHERENT IN THE PARASITIC THEORIES OF THE ETIOLOGY OF CARCINOMA.

WITHIN these last few years, in which the science of bacteriology has made such mighty strides, the etiology of many diseases, which before had been obscure, has been placed on a sound basis by the irrefutable demonstration of their bacteriological origin; and, at the present time, so many diseases have been referred to the kingdom of parasites for their etiology that it has almost seemed that ere long the most of pathology must have for its basis some of the lower vegetable or animal forms. Observing the tendency of this great current, many far-seeing pathologists have hinted at the bacteriological origin of this or that disease, and have won glory when, in the course of time, their wise predictions have been conclusively proven and universally accepted. So striking have been these revelations that it would seem that one could scarcely go amiss in surmising at etiology along this line. This enthusiasm has led a host of pathologists, who, observing the already demonstrated causes of the gumma, the tumor albus, the xyloma, the actinomycosis granuloma and many others, to seek for similar causes in other tumors of unknown origin.

The great amount of study which has been given to the subject of carcinoma has, as yet, failed to establish sufficiently the nature of the disease. The theory of Cohnheim, incomplete as it is, stands at the present time for our most advanced views on the subject. The parasitic theory of the etiology of carcinoma was long ago hinted at. In 1847 Virchow observed the peculiar minute bodies between the parenchyma cells and also within the cells themselves, which have since been identified as sporozoa.[1] This unicellular animal body has of

[1] Virchow's Archiv, Bd. 33.

late been the object of much observation. It has been given its biological place among the gregarinidæ. Pfeiffer[1] observed bodies which he called sporozoa in both sarcoma and carcinoma. This same class of parasites has been discovered in certain skin diseases, and notably those in which there is a tendency to heterogeneous proliferation of epithelial cells. Wickham,[2] Darnier,[3] Hacke,[4] Malassez and Albarran,[5] Steinhause,[6] Strobe.[7] Vincent,[8] Foa,[9] Van Henkelom[10] and Thoma,[11] have all reported such parasitic cells in carcinoma, and the first two observers have regarded them as the probable cause of the disease, though they cannot be demonstrated as etiological factors, nor have cultures or inoculations been made. On the other hand, Russel, Pifford, Schutz,[12] Cornil,[13] Hausemann,[14] Török, Ribbert,[15] Tommasoli, Duplay, Cazin and others, who have observed these bodies, incline to regard them not as parasites, but as products of cell degeneration or as karyokinetic nuclear changes.[16]

Within the past year three works on the subject, by Podwyssozki and Santschenko,[17] Sondakewitsch[18] and Noeggerath,[19] have appeared.

[1] Zeitschrift für Hygiene, 1888, III, 3: IV, 442.

[2] Archives de med. experimentale, 1890, I, 1.

[3] Centralblatt für Path. Anat., I, 682.

[4] Soc. de Biolog., Nov., 1890.

[5] Soc. de Biolog.. Apr., 1889.

[6] Virchow's Archiv, Bd. 126, s. 533.

[7] Zeigler's Beiträge, 1891, XI, Heft 1.

[8] Annales de Micrograph, 1890, II, p. 10.

[9] Gazz. degli Osp., No. 14.

[10] Centralblatt für Path. Anatomic, 1890, p. 704.

[11] Fortschrit der Medicin, 1889, p. 413.

[12] Microscopische Carcinombefunde, Frankfort, 1890.

[13] Journal de l'anat, et de physiol, 1891, No. 1.

[14] Virchow's Archiv, Bd. 123, p. 356, 1890.

[15] Deutsche med. Wochenschrift, 1891, p. 1179.

[16] Park: The Parasitic Theory of the Ætiology of Carcinoma: N. Y. State Med. Soc. Transact., 1893.

[17] Centralblatt für Bact. u. Parasitenkunde, 1892, Nos. 16–18.

[18] Annales de l'Instit. Pasteur, 1892, T. VI, No. 3.

[19] Wiesbaden: J. F. Bergmann, 1892.

The first two speak with great assurance on the presence of parasites in carcinomatous cells; though, after their exhaustive research, they conclude that neither the observers, who claim the presence of sporozoa in carcinoma, nor those who deny their presence, have sufficient ground for their dogmatic claims. Stroebe,[1] who has observed and delineated these bodies, does not feel convinced of their parasitic nature, because of the difficulty of excluding the question of nuclear degeneration.

Observations have also been made in the line of the discovery of bacteria in carcinomatous growths. Rappin claimed to have discovered a diplococcus as the cause of carcinoma, and even to have inoculated rabbits with positive results. Scheurlen[2] found a spore-forming "carcinoma bacillus," which he was able to cultivate on gelatine and potatoes. But these observations have been long since thrown aside, either on the ground of inaccuracy or the want of further proofs.

Finally, we have the elaborate researches of Adamkiewicz, just published.[3] The widespread attention which they have received, and the immediate clinical application to which they have been put, entitle them to a more complete analysis in this paper. Adamkiewicz holds that carcinoma presents all the characteristics of a chronic infectious disease, but not being able to discover the parasite of the disease, we have too readily fallen back upon the old hypothesis of Cohnheim. He refuses to recognize carcinoma cells as identical with epithelial cells, and points out that they present three forms in the course of their development. The young form is that resembling the leucocytes; in a higher stage of development they approach the epithelial cells; and, lastly, they become carcinoma cells, with their tendency to the formation of irregular projections, and finally to degeneration and disintegration. This degeneration in the later stages he regards as a feature of differentiation from the epithelial cells. He

[1] Ziegler's Beitrage, Bd. XI, Taf. I.

[2] Deutsche med. Wochenschr. 1887, No. 48.

[3] Untersuchungen über den Krebs und das Princip seiner Behandlung, 1893.

assumes that carcinomatous tissue possesses toxic properties, and proves it by inoculating animals with bits of tumor and by injecting filtrated watery extracts, producing death in a few hours or days. This special poison he has called cancroin. It seems, without doubt, to him that carcinoma is a parasitic disease. The parasite not growing on the usual culture media, he undertook the use of living tissue in its stead, and planted bits of carcinoma in the brains of rabbits.

The carcinoma cells were observed to migrate from the implanted particles in the direction of the least resistance along the clefts in the brain substance, to become implanted and form nuclei for further propagation. Therefore, he concludes that the carcinoma cells are to be regarded as living creatures, and are themselves the specific parasites of the disease. To this parasite he has given the name coccidium sarcolytes, and this is the source of the cancroin, the irritating action of which causes the changes in normal tissue.

When we now come to sum up these observations, we see the very conflicting opinions of accurate observers, and the diametrically opposite conclusions at which many have arrived. The theory of the bacteriological origin of carcinoma gave place, among those who sought for a parasitic etiology, to the sporozoa or coccidia. Against these stand the views of the great number of observers who believe that these bodies, which have been interpreted as animal parasites, are the products of disintegrated nuclei, or nuclei in the process of mytosis. The whole evidence of their parasitic nature is based upon the insufficient ground of their appearance within or among the carcinomatous cells. They have not been isolated or cultivated outside of these cells. The microscopic appearance alone is inadequate for the basing of such a conclusion. For example, I may cite the deception occurring in fat cells, by which the intra-cellular septa, when stained, present the appearance of tubercle bacilli, a thing which Orth has regarded of sufficient importance to be made the subject of an essay. The pronounced tendency of carcinoma cell nuclei to disintegrate, and the mytoses occurring in the younger cells may well account for these peculiar appearances.

The fact that certain granulation tumors are of infectious origin does not justify the conclusion that carcinoma, clinically and hystogenetically different, has a similar cause. The transplantation or infection with carcinoma cells is nothing more than can be done with the skin, periosteum or other tissues, and occurs in the benign as well as malignant growths. With the granulation tumors it is different. A secondary growth of tubercular or syphilitic tissue is not brought about by the transplantation of the cells making up the growth, but by the transplantation of the specific micro-organisms by the blood, lymph or other channels, the irritating products of which give rise to the peculiar productive inflammatory process. The cells of such a secondary deposit are by no means descendants of the cells of the primary growth as are those of carcinoma, which, when implanted remote from the mother tumor, continue to produce cells of the parent type, the pre-existing cells taking no part in the formation of the characteristic parenchyma. The only means by which secondary deposits can form from carcinoma is through this transplantation or metastasis of carcinoma cells, which is facilitated by the peculiar anatomical nature of the tumor. If, then, there are specific parasites for carcinoma, they must possess a predilection for epithelial cells, and be transmitted by the cells to the localities in which metastases develop, and yet not invade the cells of this new locality, even though they be epithelial in character. The parenchyma of a metastasis in the liver of an epithelioma of the tongue presents the peculiarities of epithelial cells of the tongue. The flat epithelial cells proliferate among the polyhedral liver cells, which play only a passive part.

It has been my fortune to observe a primary carcinoma of the liver with multiple secondary deposits. On cutting into these secondary nodules, which were scattered along the post-peritoneal lymphatics, a greenish-yellow fluid exuded which responded to the tests for bile, and the cells of these nodules were anatomically identical with liver cells. Examples of this sort, showing that in the metastases of carcinoma the parenchyma repeats the type of the epithelial cells from which the

primary growth sprang, might be indefinitely multiplied. These facts speak against the microbic theory of carcinoma, and quite refute the doctrine of Adamkiewicz, which asserts that the characteristic neoplasmic cells themselves are not epithelial cells, but are parasitic bodies. How he accounts for these bile-secreting parasites is hard to conceive. Furthermore, it is not difficult to make a section at the edge of a carcinoma, including some of the normal tissue, in which the normal epithelial cells may be traced as directly anatomically continuous with the parenchymatous cells of the neoplasm. The same thing is seen in the adeno-carcinomata so common in the stomach and rectum, in which adenomatous cells merge into the carcinomatous cells.

If the parasitic theory be accepted, it must be reconciled with the other malignant tumors, and also with the so-called benign growths which give rise to metastases, and which have so much in common with carcinoma. The fact that the carcinomata are anatomically related through the endotheliomata and peritheliomata to the malignant sarcomata on the one side, and that they are allied through the adeno-carcinomata to the benign adenomata on the other side, places another difficulty in the way of this hypothesis. This similarity may be further traced in the etiological factors strikingly common to all tumors, which may be spoken of as mechanical or chemical irritation, or influences which hinder in some way the development of cells within their normal limitations. The epithelioma of the lower lip of pipe smokers, the chimney-sweep's carcinoma scroti, the "paraffine cancer" of paraffine workers, carcinoma of retained testicle, epithelioma of the tongue opposite the sharp edge of a carious tooth, are but a few of the well-known examples. In scar tissue of the soft parts develop carcinomata or sarcomata; at the seat of fractures appear chondromata, osteomata or sarcomata; from chronically inflamed mucous membranes develop polypi, adenomata or carcinomata; and so on examples might be multiplied. The tendency of an heterogeneous proliferation of epithelial cells at the seat of a lupoid inflammation gives a glimpse of bacterial products acting as a cause of epithelial misdevelopment. In the edge of a healed gastric ulcer the

epithelium is observed to send down chains infiltrating the underlying tissue. As a rule, this carcinoma-like condition gives rise to no further growth, but when, for some reason, the physiological equipoise between the aggressive tendency of the epithelium and the resisting tendency of the surrounding cells becomes disturbed, from precisely this locality carcinoma develops.

Nor do the malignant tumors alone give rise to metastases, for multiple developments of chondromata, lipomata, fibromata, myomata, papillo-cystomata and, in fact, all the new growths, benign or malignant, have been observed to proliferate in this manner.

It would be superfluous to multiply evidence showing the etiological and anatomical features common to all tumors. No parasitic origin can be suggested for any of these excepting carcinoma; and in view of this fact, and in view of the fact that the evidences of the parasitic etiology of carcinoma are so imperfect, we must still regard the new growths as either belonging to the class of misdevelopments, or as being due to some cause exciting the fixed cells to a greater than normal activity.

The most plausible of parasitic theories is that of the sporozoa. Its right to consideration as an etiological factor of carcinoma is, however, nullified by the fact that its champions are contradicted by an equal number of equally accurate observers. The doctrine of the bacterial cause is to-day quite unchampioned; and, finally, the theory of Adamkiewicz is unnatural and illogical. The hypothesis of Cohnheim, though not histologically substantiated, still stands as accounting for many inexplicable phenomena. It is, however, within the range of the greatest probability that the cause of tumors has been sought for too wide away from the real nature of things, and that it lies nearer the ordinary and constantly operating phenomena, and not among the rarer and more remote biological possibilities. In such simple growths as clavus no far-fetched etiology is sought, but simple mechanical irritation satisfactorily accounts for the piling up of epithelial cells. May we not presume, then, that chemical or mechanical irritation, *per se*, may be a cause of carcinomatous

degeneration without complicating the etiology still more by the hypothesis that such irritation is a cause only as it impairs the cell vitality and renders it an easier prey for the specific micro-organism? The expression "irritation," for want of a better term, must stand for inflammatory processes giving rise to parenchymatous or interstitial cellular changes.

Mr. Darwin has shown that habits or induced conditions acting continuously through a number of generations finally become engrafted upon the line, and are transmitted as instincts or inherent qualities; and is it not possible that epithelial cells, which for a series of generations have propagated under such abnormal conditions as have caused and as exist in a primary carcinoma, may become endowed with the pernicious vitality which finally characterizes the metastatic growth?

JAMES P. WARBASSE.